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## Pathogenesis of Tuberculous Meningitis.

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### Introduction

Tuberculous meningitis is still one of the frequent and severe diseases especially in children, although some chemotherapeutics such as streptomycin, hydrazide, etc. have shown marked curative effect on the disease. However, despite the frequency and the importance of the meningitis, the pathogenesis itself still remains obscure and comparatively few papers have been presented about the pathological findings and the pathogenesis of the disease. In the previous publications, some opinions about this problem were recommended. Kment<sup>1)</sup> had detail investigations and stated the important rôle of the chorioide plexus in the progression of the meningitis; namely, he concluded that the tuberculous lesion primarily occurred at the plexus and then extended to the base of the brain along the periarterial lymph space. Rich and McCordock<sup>2)</sup> stated that the cerebral and meningeal tuberculomata were generally sources of meningitis. Their observations indicate that the meninges are secondarily involved by the discharge of tubercle bacilli into the cerebrospinal fluid from continuous older caseous foci such as a tuberculoma in the brain or osseous lesions of the vertebrae. On the contrary, Kubo<sup>3)</sup> stated that tuberculous lesion originated in the small arteries of the meninges and developed into the subarachnoid space.

To make the pathogenesis of tuberculous meningitis clear, the author investigated as follows: I, the autopsies of children with tuberculous meningitis between 3-month- and 11-year-old, and II, those of animals which involved the experimental tuberculous meningitis. A part of this paper has been published already as a cooperated work.<sup>4,5)</sup> In order to clarify the thesis, the author is indebted in using the pictures which appeared in the former report.

### I. Reports of Cases.

These works were based on the study of 10 cases of tuberculous menin-

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gitis and 1 case of miliary tuberculosis at the Department of Pediatrics, Kyoto University. On the examination of the brain, the connection of the blood vessels to the tuberculous lesions in the meninges was mainly observed in order to acquire the stereographic findings. The materials were fixed with ethanol or 10 per cent formalin. The meninges were stripped off from the brain with dental pincette, extended on the slide glass, stained by hematoxylin-eosin and Ziehl-Neelsen solution and mounted with balsam. The author will call the specimens as "spread specimen" hereafter. The brains were continuously cut thinly into pieces about the size of 0.5 cm. to investigate the older caseous foci.

**Case I :** K. S. a boy, 3-year- and 6-month-old. At the end of Feb. 1950, he began to cough frequently and gradually lost the weight. The Mantoux reaction was negative. On May 12, 1950, temperature rose to 39°C-40°C. He did not feel well and lost appetite. Five days before his admission on May 29, he began to fall into drowsiness. No sign of vomiting and convulsion was observed.

His past history : He was born with the weight of 3.2 kg. and was fed on mother's milk. He made complete alactation by 18-month-old. No tuberculous history was found in his family circle.

He was faint and looked pale with temperature 39°C, pulse 120 a minute, and respiratory 30 a minute. The stiff-neck and the rigidity of the extremities were observed. The deep reflexes in the lower extremities did not react. The heart did not enlarge by percussion, and no murmurs and non arrhythmias were detected by auscultation. On the examination of the chest, no râles were heard all over the chest and the sound was clear. The pupils were unequal and the right was larger than the left. No change was found in urine and stool. On the rentgenographic findings of the chest, no miliary density, nor the shadow of the enlarged paratracheal lymph node were present. On the examination of the abdomen, neither the liver nor the spleen were palpable. The blood test showed erythrocytes  $411 \times 10^4$ , hemoglobin amount 74 per cent, leucocytes 16,670, neutrophile leucocytes 38.4 per cent, lymphocytes 57.2 per cent, monocytes 2.0 per cent, eosinophile leucocytes 1.6 per cent, basophile leucocytes 0.4 per cent.

The cerebrospinal fluid specimen obtained at this time showed clear under increased pressure, having a slight decrease of sugar and protein of 0.99 per cent according to the Brandberg's method. Pandy's test showed positive reaction and tubercle bacilli were found. Five days after his admission, he died gradually falling into delirium and having involuntary movement in the right extremities.

Autopsy : The brain weighed 1,120 gm. and revealed hyperemia. There

were a light-green gelatinous exudate on the base of the brain and numerous miliary tubercles in the whole meninges. In the lung, there were miliary tuberculous lesions and two swollen paratracheal lymph nodes about the size of a finger-tip. Miliary tuberculous lesions were also investigated widely in the spleen but not in the liver and the kidney. Tuberculous ulcers were seen in the intestine.

**Caes II :** Y. N. an 8-year-old boy. On May 16, 1950 he complained of high temperature with headache after returning from his excursion trip. For several days the temperature continued to go up and down. On May 21, 1950 he had acute headache, nausea and vomiting. Mantoux test taken on May 12, 1950 showed positive reaction.

His past history : He had rubeola and measles when he was 3-year-old.

On May 26, 1950 he was admitted to the hospital. The physical examinations showed temperature 37.4°C, the pulse rate 70 a minute and his respiratory rate 28 a minute. He did not look like ill by his appearance. Nothing was found wrong with the chest on the physical examination. The X-ray findings showed a primary lesion and the enlargement of the regional lymph nodes. There was no development of stiffneck, nor rigidity of extremities. The deep reflexes in the lower extremities did not accelerate. The cerebrospinal fluid specimen obtained at this time showed clear under a pressure of 120 mm. H<sub>2</sub>O, having a slight decrease of sugar, containing small lymphocytes 47, large lymphocytes 10, leucocytes 9 and protein 0.99 per cent. Tubercle bacilli were proved with culture and the "spider's web" was formed. After his admission, the general conditions gradually became worse. Two weeks later, he had convulsion and gradually lost his consciousness. The general conditions took a turn for the worse with the stiff-neck and the rigidity of the extremities. By this time, there also appeared Babinsky's and Kering's signs. His pupils dilated and they began to lose the reaction to light. Finally he died on June 27, 1950.

Autopsy : The weight of the brain was 1,450 gm. It revealed miliary tuberculosis in the meninges, lung, liver, spleen and kidney.

**Case III :** Y. A. a 2-year-old boy. On May 25, 1950, he suffered from an adenopathia on his left neck, accompanied by the temperature of 38°C. The adenopathia disappeared after a week, however, the temperature had continued until the admission to the hospital on June 28, 1950. On June 14, 1950 he had vomiting and nausea in the early morning. On June 23, 1950 he lost his physical strength and fell into drowsiness. He continued to refuse food.

On June 28, 1950, he entered the hospital. On the physical examinations, his consciousness was not clear and he looked pale with a pulse rate of 146 a minute, and a respiratory rate of 45 a minute. On the examinations of the

chest, generally the sound was normal, but it was weak on the lower right back. As to the abdomen, the spleen was nonpalpable and the liver was palpable for 3 cm. The fontanelle was bulging to extent of 2×2 cm. The pupils showed normal reaction to light. The knee reflex was accelerated. The neck was stiff. There was no Kernig's sign by this time. Lumber puncture revealed a clear fluid with 72 cells per cmm. containing lymphocytes 23, and neutrophile leucocytes 49, under increased pressure, having decreased sugar, and containing protein 0.165 per cent according to Brandberg's method. At this time, the Pandy's reaction was extremely positive and formed a "spider's web" which contained tubercle bacilli. On July 10, 1950, he suffered chicken pox. He entirely lost his consciousness and began occasional convulsion. On July 11, 1950, the temperature rose to 40°C, the pulse rate was 214 a minute and the respiratory rate was 80 a minute. Convulsion occurred frequently. The deep reflexes were not present. He began the Biot's respirations and finally died on July 13, 1950.

**Autopsy :** The tuberculous lesions with a light green gelatinous exudate were revealed on the base of the brain. Miliary tuberculous lesions were found in the brain, lung, and spleen, but not in the liver and kidney. The brain was 1.357 gm. in weight, and revealed marked edema and hyperemia. There was a primary focus and the several enlarged regional lymph nodes about the size of a finger-tip in the lung.

**Case IV :** M. K. an 11-year-old boy. On July 4, 1950, he complained of a headache with a slight degree of fever. By the administration of streptomycin, 0.5 gm. per day for 11 days, he became well. On July 24, 1950, he had stomachache, vomiting occasionally and felt very sick. On August 16, 1950, he suddenly lost consciousness and gnashed his teeth. He was talking in delirium. The next day, he was admitted, but he died. The physical examinations reported that slight fever, bony outlook of his face, vague consciousness and the slow, unclear responses continued. No unusual sign was found in the abdomen and the chest. The knee reflex accelerated. The slight stiff-neck and the Kernig's signs were revealed. The X-ray findings indicated no miliary tuberculosis. The cerebrospinal fluid specimen obtained at this time showed clear under extremely high pressure, with 55 cells per ccm., lymphocytes 75 per cent, decreased sugar, protein 0.016 per cent, and both Pandy's reaction and tubercle bacilli tests were positive. The physical examinations and the X-ray film of the chest showed no changes, no miliary tuberculosis nor primary focus. Since his admission, he had been in delirium. His pupils showed no reaction to the light and no anisocorie. Five days after his admission, he showed typical pedis clonus, Kernig's sign and stiff-neck. After gradually getting worse in his general condition, he finally died on August

27, 1950.

Autopsy : The brain weighed 1,265 gm. and its base was covered by a light green gelatinous exudate. The miliary tubercles were found in the meninges, lung, and spleen. In the intestine, there were the tuberculous ulcers and tubercles.

**Case V :** T. T. a 3-year-old boy. On June 8, 1950, his face looked pale and he lost strength. On June 28, 1950, suddenly the temperature went up and a week later he began to complain of dyspnea and abdominal pain. On July 8, 1950, he entered the hospital. The X-ray film of the chest showed miliary tuberculosis. He was treated with streptomycin and teben, and his condition seemed to be getting better by this treatment. On July 23, 1950, erythema nodosum began to appear in the lower extremities. Since then his general condition became better and the miliary tubercles in the X-ray film also disappeared. Five months after his admission, his condition became worse with a high fever, 40°C and dyspnea and he died on Dec. 23, 1950.

Autopsy : The brain weighed 980 gm. and its base was covered by a light green gelatinous exudate. In the lung, there was primary focus and the enlarged regional lymph nodes, and also the the miliary tubercles were dotted all over the organ. On the microscopic findings, there were miliary tubercles in the brain, lung, liver, spleen, pancreas and thyroid gland.

**Case VI :** R. F. a 2-year-old boy who suddenly fell into the illness with febris and vomiting on August 24, 1950. Two weeks later, he had a convulsion. Immediately he was treated with streptomycin and PAS with the diagnosis of tuberculous meningitis. Soon he began to appear as if he had recovered. On Nov. 4, 1950, he lost the consciousness and two weeks later he showed the signs of incontinence. He entered the hospital on Nov. 24, 1950. On the X-ray findings showed a mottling in the upper part of the right side of the lung. He showed the stiff-neck and pedis clonus. He also developed rigidity in his extremities and showed positive Brudginski's and Kernig's signs. The spinal fluid was clear with 94 cells per cmm. lymphocytes 20, neutrophile leucocytes 74, decreased sugar and protein 0.195 per cent. Two months after his admission he died.

Autopsy : The pathologic findings revealed tuberculous meningitis with miliary tuberculosis in the lung, liver, spleen, kidney and tonsil. Hydrocephalus internus was found in the brain. On the microscopic examination, the same results were revealed.

**Case VII :** S. W. a 6-year-old boy was admitted to the ward on Oct. 20, 1951 having fever, vomiting and anorexia. Tuberculin test, repeated as a part of the routine examinations, showed doubtfull positive reaction (10×7 mm). The neurological examinations were still normal. The spinal fluid

was clear, with increasing pressure with 189 cells per cmm., containing 86 lymphocytes and 103 neutrophile leucocytes. There was a decrease of sugar content and increase of protein of 0.165 per cent. On culture, tubercle bacilli were proved. He did not fall into drowsiness until Dec. 20, 1951 when he lost consciousness and he fell in the complete status of drowsiness on Jan. 11, 1952, two days before his death.

**Autopsy :** The white gray tubercles dotted, in general, in the meninges and the intensity was strong especially in the base of the brain. In the lung, the primary caseous focus and the enlarged regional lymph nodes were found (in the upper part of the left lobe). The miliary tubercles were slightly recognized in the spleen, while they were not found in the liver and the kidney.

**Case VIII :** a 4-year-and 7-month-old girl. On Feb. 14, 1950, she had vomiting and headache, accompanied by a temperature between 37°C and 38°C. On Feb. 27, 1950, she lost her consciousness and entered the hospital on the same day. Her Mantoux reaction was negative on May 12, 1950, although she was injected BCG last year of her admission. Her pulse rate was 95 per minute, and her respiratory rate was 30 per minute. On the neurological examinations the Kernig's sign was positive and there was no the stiff-neck, nor the rigidity in the extremities. Both Babinsky's sign and pedis clonus were present on the lower right extremity and they were absent on the other extremity. The right pupil showed no reaction to light, though the left pupil showed it very slowly. The spinal fluid was under increased pressure, clear, showed 111 cells per cmm. 66 per cent lymphocytes, decreased sugar, protein 0.66 per cent, and the tubercle bacilli were proved with culture. In spite of the administration of streptomycin intramuscularly and intrathecally, she died after 28 days from her admission.

**Autopsy :** The miliary tubercles were revealed all over in the meninges and a greenish yellow, creamy gelatinous exudate in the base of the brain. No other pathological findings were recognized except for several rice-sized caseous lesions in the mesenteric and the hilar lymph nodes.

**Case IX :** A. A. a 2-year-old boy. On Jan. 16, 1950, he lost consciousness without vomiting or convulsion. There was no changes in the chest on his physical examination. He showed a stiff-neck and a positive Kernig's sign. On March 4, 1950, his consciousness seemed to be gradually recovered, but he lost his sight. His pupils dilated showing no reaction to light. He continued the better or worse conditions alternatively and fell into unconsciousness again on May 13, 1950. The X-ray findings of the chest showed no abnormality but hilar adenopathy. At that time he developed the stiffneck and the rigidity of the extremities. He died on May 25, 1950.

Autopsy : On the brain, the miliary tubercles were presented in the meninges and white, flocky exudate in the base of the brain. In the lung, a primary focus was not found, but several pea-size hilar lymph nodes were present. The miliary tubercles were found in the spleen and lymph nodes.

**Csea X :** F. K. an 8-month-old girl. On March 13, 1950, she began to lose her appetite and fell into drowsiness. She entered the hospital on March 23, 1950. She continued the same conditions and finally became unconscious. On the physical examinations, both swollen liver and spleen were palpable. The clear fluid showed increased pressure, and 65 cells per cmm., 61 per cent lymphocytes, decreased sugar and protein 0.231 per cent. Tubercle bacilli were proved with culture. The fontanelle was not bulging. The stiff-neck and Kernig's sign appeared two days before her death. She developed pedis clonus and the rigidity of the extremities on April 1, 1950. The pupils showed no reaction to light, and convulsion occurred occasionally. She died two days later.

Autopsy : In the brain, there was much white purulent exudate in its base and numerous miliary tubercles in the meninges. Miliary tuberculous lesions were revealed in the lung, spleen, liver, kidney, etc., and the size of its tubercle was about as big as a pea.

**Case XI :** S. H. a baby girl, about 3-month-old. She entered the hospital because of dystrophia; she weighed 2.1 kg. and was very thin. There were no special symptoms on the physical examinations. After her admission, her liver and spleen gradually began to swell. The blood test showed erythrocytes  $510 \times 10^4$ , hemoglobin amount 73 per cent, leucocytes 23,000 neutrophile leucocytes 51.2 per cent, lymphocytes 34.0 per cent, monocytes 4.0 per cent, and eosinophile leucocytes 0.8 per cent. Both Mantoux and Wassermann reaction were negative. She died 46 days after admission without showing the neurological findings or a high temperature.

Autopsy : The pathological findings revealed general miliary tuberculosis; namely numerous disseminated tubercles were present in the lung, liver, spleen, kidney and mediastinal and mesenteric lymph nodes.

Though the appearance of her brain was clear and microscopic section showed no lesion, the spread specimen revealed miliary tubercles suspended in clusters as in Fig. 5 only in the base of the brain.

In the cases mentioned above, the pathological pictures of the tuberculous lesions can be distinguished from miliary nodules and diffuse perivascular exudation through the observations of the spread specimens of the meninges which were stripped off from the brain and stained.

The nodules were suspended in clusters around small blood vessel and their sizes were between  $200\mu$ . and  $800\mu$ . in diameter. It seemed to be



Table 1: Pathological findings of human cases.

Case No.		I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Name		K.S.	Y.N.	Y.A.	M.K.	T.T.	R.F.	S.W.	H.K.	A.A.	F.K.	S.H.
Age		3y.	8y.	2y.	11y.	3y.	2y.	4y.	9y.	2y.	6y.	3m.
Sex		m	m	m	m	m	m	m	f	m	f	m
Duration of meningitis (day)		27	45	30	55	153	159	100	28	129	20	—
SM.* doses (gm.)		0	2.0	6.5	8.0	57.0	49.0	63.0	6.0	13.0	2.0	0
Lung	miliary tubercle	###	##	+	##	+	+	+	—	##	##	##
	caseous foci	—	—	—	—	—	+	+	+	+	##	##
	cavity	—	—	—	—	—	—	—	—	—	+	—
Pleura		—	+	—	+	—	+	—	+	—	+	—
Liver		—	+	—	—	—	+	+	—	—	+	##
Spleen		##	+	+	+	—	±	—	—	##	+	##
Kidney		—	+	—	—	##	—	—	—	—	+	##
Intestinum		+	—	+	±	—	—	—	—	—	+	+
Lymph nodes	mediastinal	##	##	+	##	+	+	+	##	+	##	+
	mesenterial	##	—	+	+	±	+	—	##	—	##	+
Meninges	convex	##	±	±	+	##	+	—	+	±	##	—
	base	##	+	##	##	##	##	##	##	##	##	+
	blood vessel	+	—	##	##	##	+	##	##	+	##	—
Brain	invasion from meninges	±	##	##	+	##	+	+	+	+	##	—
	solitary tubercle	+	+	—	—	—	+	—	+	—	—	—
	encephalo-malacia	—	—	+	—	+	—	+	##	##	—	—

\* SM. ... Streptomycin

something corresponding to the tubercle of miliary tuberculosis. This was also found thoroughly in all the meninges of tuberculous meningitis and it is worth to mention that several of nodules were found in the base of the brain in a case of miliary tuberculosis without meningitis. Namely, miliary tuberculosis on the meninges seemed to form the shape of the nodule while the latter, exudation, characterized the typical tuberculous meningitis. A great number of miliary nodules was found in the vaulted portion of the brain but a little was in the base, where exudation existed tremendously.

## II. The Experimental Study

Many investigators<sup>6,7,8,9,10,11)</sup> have already attempted to produce experimental tuberculous meningitis by means of the discharge of bacilli into the blood stream or directly into the subarachnoid space, and also they have used allergic or non-allergic animals. The pathological findings of meningeal lesions were observed on various cases of experimental meningitis and found to be similar to those of human cases.

First of all, the study on direct infection of the meninges was attempted by the cisternal puncture (Foot<sup>6)</sup>, Austrian<sup>8)</sup>, Soper<sup>9,10)</sup> and Rich have produced meningitis in this manner). The histological description of the lesions in these reports have been either very sketchy or completely lacking, but it is important to study the formation of lesions in the cases of meningitis. In order to observe the formation of lesions by discharge of bacilli in various way, the author made the following experiments.

### (1) Intrathecal Inoculation of Tubercle Bacilli.

A series of 6 allergic and 3 non-allergic rabbits were employed for the study. As for tubercle bacilli, virulent bovine (B I) bacilli which were preserved at the Tuberculosis Research Institute, Kyoto University were used. The animals of the allergic group were injected subcutaneously with 0.2 mg of bacilli, and after thirty days, they showed positive Roemer reactions. All animals of allergic and non-allergic groups were injected with a suspension, 0.1 ml. containing 1 mg. or 0.05 mg. B. I. bacilli, into the subarachnoid space directly by the cisternal puncture. The allergic animals died on the 3, 8, 9 and 12th days after the inoculation, and two others were killed on the 7th and 32nd days. Since the non-allergic animals did not die, they were killed by air embolism on the 8th and 12th days. Then, we made an autopsy and fixed the viscera with ethonol or 10 per cent formalin. Each viscera except the brain showed the slight tuberculous lesions.

Table 2 : Pathological findings of employed rabbit meninges.

		allergic group						non-allergic group		
Number of animals employed		12	15	14	33	11	34	21	5	22
Doses of bacilli injected into sub-arachnoid space (mg.)		1	1	1	0.05	1	0.05	1	1	1
Survival duration (day)		3d*	7k**	8d	9d	12d	34k	7k	8k	12k
Meningeal finding	perivascular cell infiltration	+++	+++	+++	+++	+++	++	++	++	++
	miliary tubercle	—	—	—	—	—	±	—	—	—
	hemorrhage	+	±	—	—	—	—	—	—	—
Cell components of inflammatory reaction	neutrocytes	+	±	±	—	—	±	—	—	—
	monocytes	+++	+++	+++	+++	+++	++	+++	+++	+++
	lymphocytes	++	++	++	+	+	++	+	++	+
	plasma cells	+	+	—	—	—	—	—	—	+

d\* die

k\*\* killed

The findings of the meninges are shown in Table 2.

In the pathological findings of both the groups, there was no great distinction. The only quantitative difference is shown in Table 2. This lesion was mainly a monocytic reaction, polynuclear leucocytes being added at the beginning and plasma cells and lymphocytes later.

This figure of meningeal lesion shows the diffuse perivascular infiltration which was seen as in human cases, and is lacking in the so-called tubercle figure. These were not shown clearly by the paraffin sections. It was of considerable interest that the bacilli in the cerebrospinal fluid may cause this perivascular cell infiltration. In the brains of two rabbits, round foci with cell infiltrations contained tubercle bacilli were found. The tubercle bacilli admitted into the spinal fluid might cause the infiltration invading into the brain through the "Virchow-Robin's space".

## (2) Intravenous Inoculation of Tubercle Bacilli.

For this examination, 6 rabbits were employed and 0.2 mg. of tubercle bacilli were injected subcutaneously. Thirty two days after the injection,

the Roemer reaction turned into positive, then 0.1 ml. of 5 per cent old tuberculin was intrathecally administrated by cisternal puncture. Immediately after that, 1 mg. of tubercle bacilli suspended in 2 ml. of physiological saline were intravenously into the V. auricularis.

Result : The rabbits showed no peculiar change in their appearance and had good appetite. Twenty seven days later, they were killed by air embolism. On the microscopic findings no change was found in the brain, though a few miliary tubercles were seen in the liver, lung and spleen. In the spread specimen, explained before, round and localized nodules were recognized along the small blood vessels as shown in Fig. 6, and Fig. 7, and these nodules were composed of mainly monocytes being occupied by epithelioid cells in the center and surrounded by a few lymphocytes. As a result of these experiments, it is concluded that the miliary nodules of the animals corresponded to those of human cases, and these nodules were due to the hematogenic dissemination of tubercle bacilli.

#### Discussion

On the study of the pathogenesis of tuberculous meningitis, the problem whether this disease is due to an initial installation of bacteria into the meninges (Huebschmann<sup>13)</sup>, Askanazy<sup>14)</sup>, Kubo<sup>3)</sup>, etc.) or is due to a secondary dissemination from a preexisting lesion in the brain (Rich, McCordock<sup>2)</sup>, Schwarz<sup>12)</sup>) is still a debatable question. According to the results of the tuberculin test in infants examined periodically by Kozuma<sup>15)</sup>, it is apparent that tuberculous meningitis develops within 6 months after the tuberculin reaction turned to positive from negative. This is opposite to the theory that tuberculous meningitis develops from the secondary dissemination of older caseous foci.

The recent studies of Choremis<sup>16)</sup> and his coworkers have reported that the bacteremia steadily continued during the pathological evolution of the primary complex : For example, the bone marrow cultures from each patient in children suffering from various forms of tuberculosis, showed positive results in 23.2 per cent of the cases with a fresh primary complex and in 50 per cent of the cases with tuberculous meningitis or miliary tuberculosis. This high percentage of positive culture result justifies the belief that the conception of the primary complex is too limited and should be signified in a more dynamic sense. The periodic or continuous bacteremia, which is accompanied by the pathological evolution of the primary complex should be considered to be responsible for the extension of the tuberculous lesions and the occurrence of tuberculous meningitis during that stage. The bacteremia, also, easily explains the existence of tubercle bacilli

in the cerebrospinal fluid in the stadium of the primary complex, and much more frequently in the case of miliary tuberculosis, with or without very slight pathological findings of the fluid.

In author's opinion, the presence of tubercle bacilli in the cerebrospinal fluid does not always indicate a disease of the meninges. The first stage in the pathogenetic circle of tuberculous meningitis is out of proportion to the extent of the visible, cerebral lesions found at autopsy. Namely, the clinical manifestations of the disease are not a consequence of tubercle formation, but are rather the result of the collateral inflammation and perifocal infiltration that accompanies them.

It has been a common knowledge that the meningitis could not be developed easily by intravascular injection of tubercle bacilli in the experiments. And the injection of tubercle bacilli into the carotis artery is not desirable because of the possibility to cause the obstruction of bacilli in the blood vessels of the brain and to form the miliary tubercles in the parenchym of the organ. Administating old tuberculin into the cerebrospinal fluid by cisternal puncture and injecting tubercle bacilli into the Vena auricularis of the animals at the same time, the author succeeded in making the first tubercle experimentally in the meninges. This experiment proved that the tubercle was due to the hematogenous installation of the bacilli on the vascular wall.

Schuermann<sup>17)</sup> made an observation on the similar nodules in the meninges of the infants which showed transitory meningismus in his report on Lübeck accident and insisted that their death was not due to meningitis but to the other tuberculosis. He made the similar specimen as above mentioned and recognized very small nest-like cellular infiltration which was formed by lymphocytes and macrophages and adhered closely to the blood vessel in the meninges, sometimes showing tubercle figure or even caseous figure. He did not always recognized the lesions in all cases with clinical meningismus, and, on the contrary, sometimes recognized it in other cases without meningismus.

### Summary

The observations on the spread specimens of 10 cases of tuberculous meningitis and 1 case of miliary tuberculosis revealed that the lesion of the meninges consisted of miliary tubercles and diffuse perivascular exudation. The former is caused by hematogenous installation of tubercle bacilli, while the latter is due to the bacillary dissemination in the cerebrospinal fluid. These were proved by the two kinds of experiments of the injection

of tubercle bacilli both intravenously and intrathecally. Tuberculous meningitis is pathogenetically regarded as dissemination in the meninges caused by the bacilli discharged into subarachnoid space from the miliary tubercle, and the typical clinical symptoms of tuberculous meningits is characterized by its collateral inflammation or diffuse perivascular exudation.

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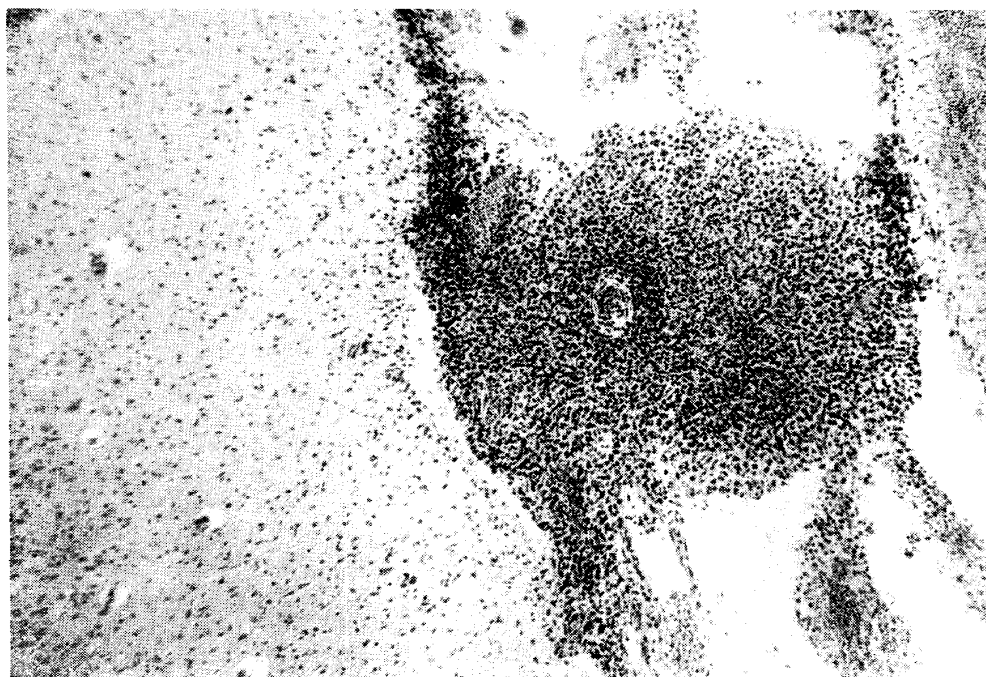


Fig. 1 Tubercle nodule in the meninges of the case X. A section specimen.

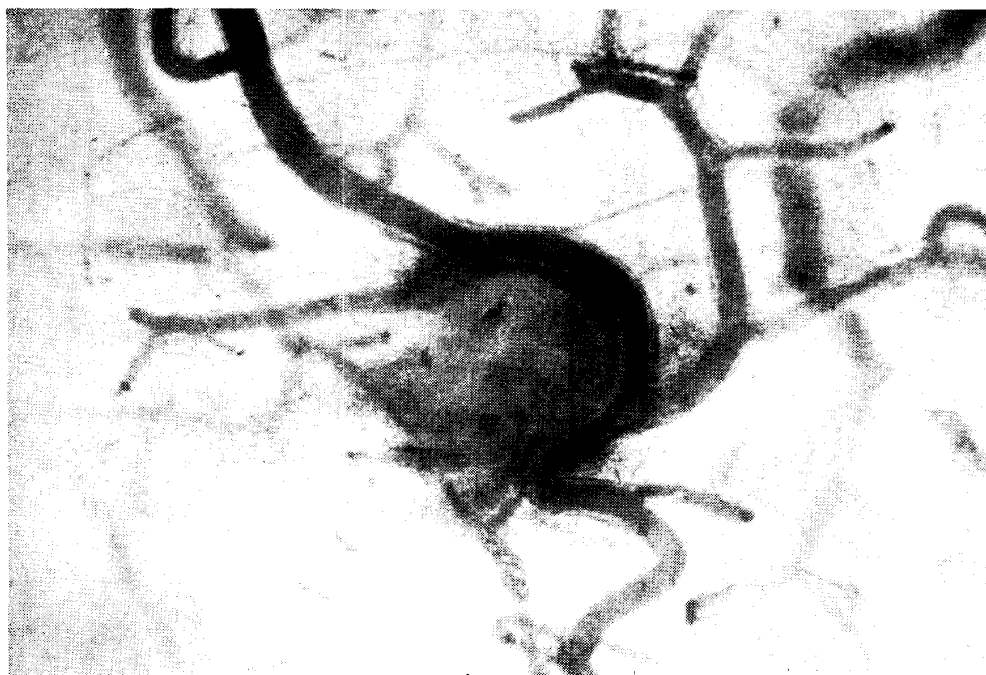


Fig. 2 Tubercle nodule in the meninges of the case III. A spread specimen.

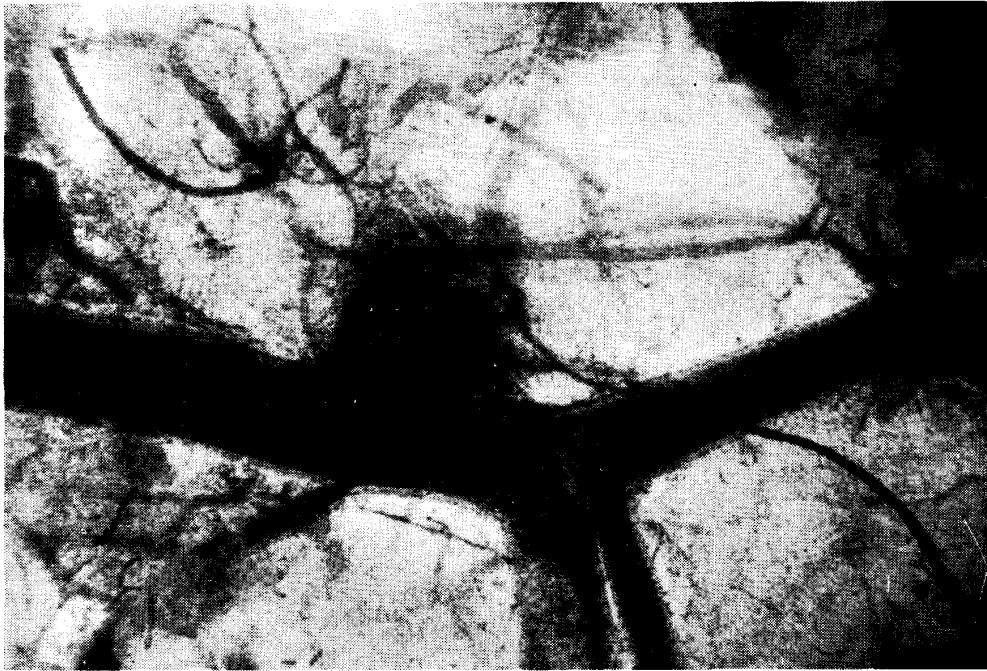


Fig. 3 Tubercle nodule in the meninges of the case I. A spread specimen

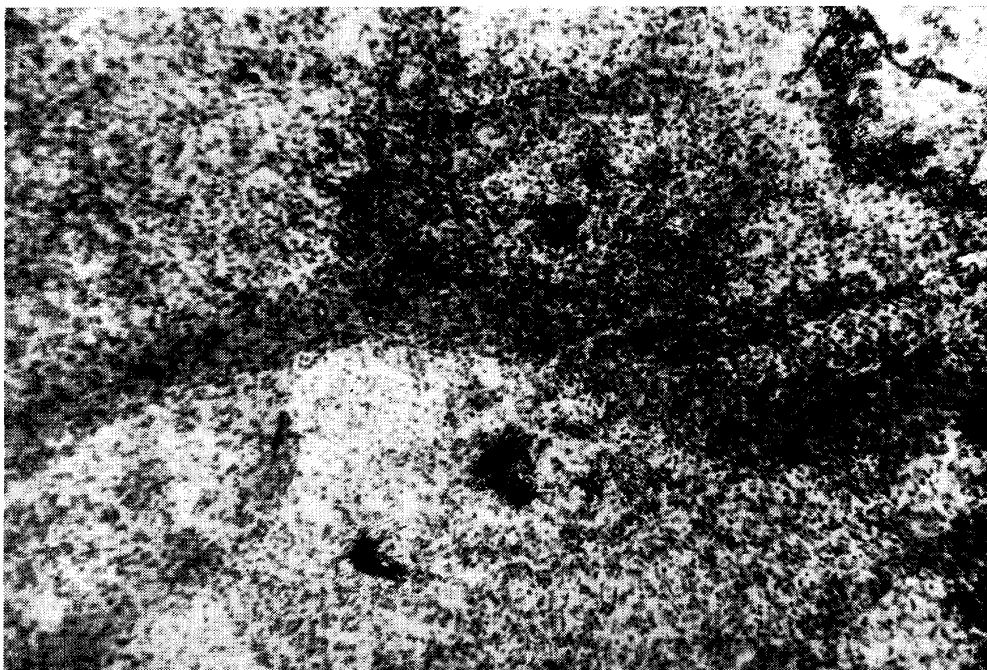


Fig. 4 Perivascular exudate in the meninges of the case I. A spread specimen.





Fig. 5 Miliary tubercles in the meninges of the case XI. A spread specimen.



Fig. 6 Tubercle nodule in the meninges of employed rabbit which was injected tubercle bacilli intravenously. A spread specimen.

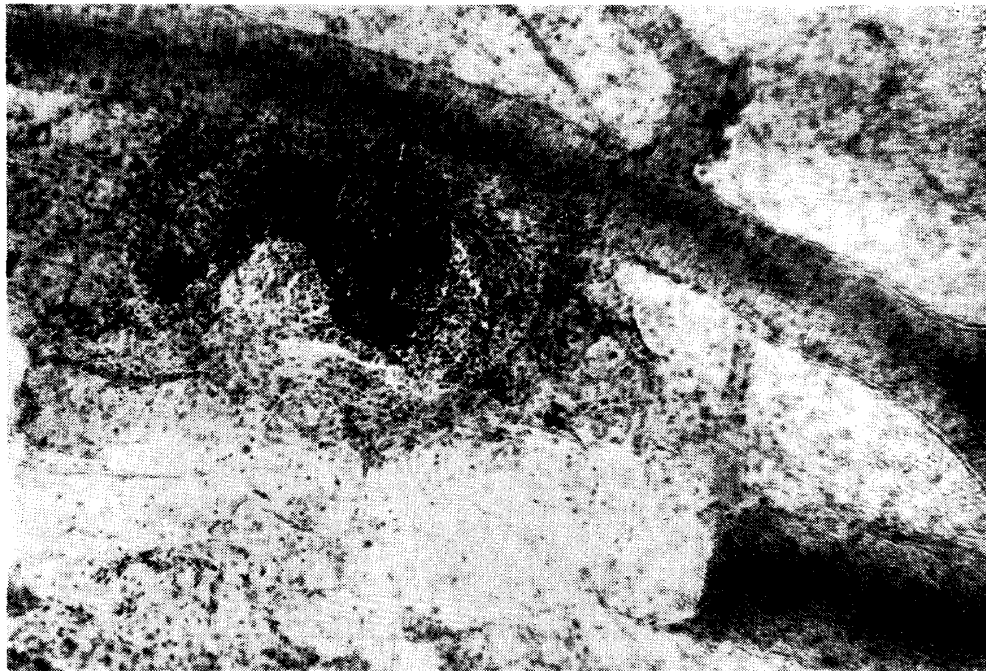


Fig. 7 Tubercle nodule in the meninges of employed rabbit which was injected tubercle bacilli intravenously. A spread specimen.

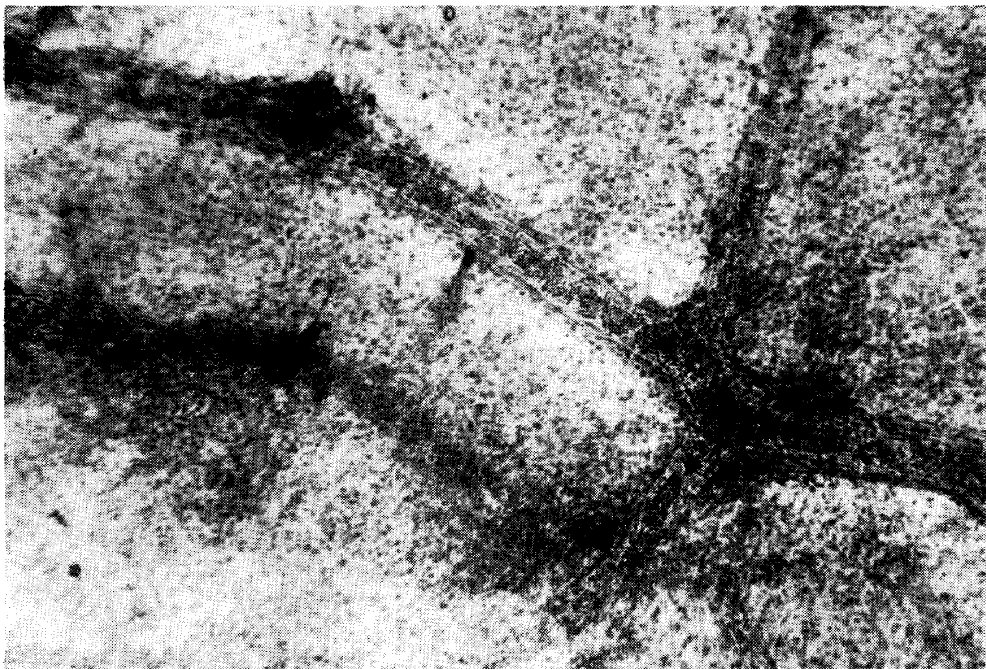


Fig. 8 Perivascular exudation in the meninges of employed rabbit which was injected tubercle bacilli intrathecally. A spread specimen.